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Original article

Serum fasting GLP-1 and GLP-2 associate with intestinal adaptation in pediatric onset intestinal failure

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SUMMARY

Aim: Glukagon-like-peptide-1 (GLP-1) and -2 (GLP-2), produced by intestinal L-cells, are key hormones regulating intestinal transit, secretion, absorption, and mucosal growth. We evaluated naïve fasting serum GLP-1 and GLP-2 levels in pediatric intestinal failure (IF).
Methods: Fifty-five IF patients with median age 4.2 (IQR 1.3–12) years and 47 matched healthy controls underwent measurement of fasting serum GLP-1 and GLP-2.
Results: Serum GLP-2 [19.9 (13.8–27.9) vs 11.6 (7.0–18.6) ng/mL, $P < 0.001$], but not GLP-1 [6.1 (4.0–15.7) vs 6.4 (3.9–10.7) ng/mL, $P = 0.976$], levels were increased in IF patients. Serum GLP-2 concentrations were higher in patients with small bowel-colic continuity [21.1 (15.0–30.7) ng/mL] compared to patients with an endostomy [10.4 (6.6–17.9) ng/mL, $P = 0.028$], whereas no association with preservation of ileum or ileocecal valve was observed. During PN delivery, GLP-2 inversely associated with remaining small bowel length ($r = -0.500$, $P = 0.041$) and frequency of PN infusions ($r = -0.549$, $P = 0.042$). Serum GLP-1 levels were lower in patients receiving PN currently [4.1 (2.8–5.1)] compared to patients, who had weaned off PN [6.5 (5.1–21.1), $P = 0.005$], and correlated positively with duration of PN ($r = 0.763$, $P = 0.002$) and negatively with percentage parenteral energy requirement ($r = -0.716$, $P = 0.006$).
Conclusions: In pediatric IF, serum GLP-2 levels increase in patients with small bowel-colic continuity proportionally to the length of resected small intestine. Increase in serum GLP-1 and GLP-2 levels paralleled reducing requirement for parenteral support. These findings support regulation of intestinal adaption by GLP-2 and GLP-1 in children with IF.

1. Introduction

Intestinal failure (IF) results from a major bowel resection or congenital defect, leading to decreased intestinal absorptive area and malabsorption, rapid intestinal transit, and need for long-term parenteral nutrition (PN) to sustain adequate nutrition, growth and survival [1]. Following a massive small intestinal resection, intestinal adaptation, which involves a series of changes in intestinal morphology, function, and regulation, efforts to compensate for the loss of functional intestinal surface area, allowing gradual weaning of PN [2,3]. Intestinal adaptation is mediated by several endocrine hormones, including glucagon-like peptides (GLP) 1 and 2 synthesized by enteroendocrine L-cells of the distal small intestine and colon [4–6]. GLP-1 inhibits gastric emptying and small intestinal and colon motility [7,8]. GLP-2 is shown to slow proximal intestinal motility, increase mesenteric blood flow, reduce gastric secretion, and to act as a trophic agent for the small intestinal mucosa improving nutrient absorption [9–11]. In patients with IF, lack of feed-stimulated GLP-2 response may lead to poor intestinal adaptation [4,5,12]. Discovery of enterotrophic effects of GLP-2 has led to novel emerging treatment options in patients with IF [13,14]. A GLP-2 analog teduglutide has been shown to improve nutrient and fluid absorption, endorse mucosal hyperplasia, and decrease PN requirement in IF patients [13,15,16].

In this study, we hypothesized that serum GLP levels are reflected by the extent and location of intestinal resection, intestinal continuity and PN requirement in pediatric onset IF. To test these hypotheses, we cross-sectionally measured fasting serum GLP-1 and GLP-2 levels in patients with pediatric onset IF and in controls matched for age and gender to investigate their relationships with intestinal adaptation during PN delivery and after weaning off PN.

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2. Methods

2.1. Ethics

This study was approved by the Helsinki University Central Hospital ethics committee and the Institutional Review Board. A written informed consent was received from all patients and controls or their caregivers before any procedures.

2.2. Patients

Medical records of all patients with pediatric onset IF treated by our rehabilitation program in Children's Hospital, Helsinki University Hospital from 1984 to 2014 were reviewed. In total, 72 eligible patients were identified of which 55 (76%) patients participated in this cross-sectional study, including clinical examination and laboratory tests. An informed written consent was received from patients and/or their parents.

For this study, IF was defined as over 50% resection of the small bowel or a duration of PN over 30 days [17,18], and patients with a primary intestinal dysmotility disorder such as Hirschsprung disease with less than 50% of age-adjusted small bowel length remaining were categorized to short bowel syndrome group. Our management protocol for IF has been reviewed recently elsewhere [19,20].

2.3. Controls

Forty-seven age and gender-matched healthy children and young adults without any renal, endocrinological, hepatobiliary or gastrointestinal disease, were used as controls. Their age [6.4 years (4.2–12), P = 0.091] and sex (boys:girls, 35:12, P = 0.144) distributions were comparable to patients.

2.4. Baseline data

Baseline patient data, including amount and composition of PN during 3 months preceding serum GLP-1 and GLP-2 measurement, surgical procedures and anatomy of the remaining bowel were collected from the patient records. Percentage of age-adjusted small bowel and colon length was calculated based on age-specific normal values [21]. The weight and height were expressed as z-scores. Body-mass index (BMI, in kg/m^2; weight divided by the square of height) was calculated for adults and Finnish reference value-based BMI-for-age was calculated for children over two years of age [22].

2.5. Laboratory tests

Blood samples were drawn after overnight fast, prepared with centrifugation and stored to −20 °C until analyzed. Quantification of serum GLP-1 and GLP-2 were performed with the Human GLP-2 (YK141) and GLP-1 (YK160) EIA kits (Yanaihara Institute Inc., Shizuoka, Japan) according to the manufacturer's instructions. The intra-assay and inter-assay CV (%) were 4.7 and 9.6 for GLP-1 and 3.0 and 14.3 for GLP-2, respectively. Serum citrulline, a marker of enterocyte mass, was measured by using an automatic amino acid analyser (Biochromon 30 Physiological and Midas Autosampler, Biochromon Limited, Cambridge, England) as described previously [23].

2.6. Statistical analysis

Descriptive statistics are expressed as median (IQR) unless otherwise stated. For multiple comparisons Kruskall Wallis test was used, followed by post hoc Mann Whitney U test when Kruskall Wallis test reached statistical significance. For pairwise comparisons Mann Whitney U test and Fisher's exact test was used. Associations were tested with Spearman rank correlation test. Statistical significance was set at 0.05.

3. Results

3.1. Patient characteristics

Patient characteristics are shown in Table 1. Causes of IF included necrotizing enterocolitis (n = 23), midgut voluvulus (n = 10), small bowel atresia (n = 9), extensive Hirschsprung's disease (n = 7), chronic intestinal pseudo-obstruction (n = 5), and gastroscisis (n = 1). Patients currently on PN were younger, had

Table 1
Patient characteristics.

	All patients	Patients on PN	Patients weaned off PN	P-value
N	55	17	38	
Boys		10	23	1.000
Age	4.2 (1.3–12)	1.0 (0.3–4.6)	7.7 (3.1–17)	**0.001**
BMI	18.5 (16.9–20.0)	20.0 (18.5–22.1)	18.3 (16.5–19.4)	0.181
Weight z-score	−0.8 (−1.5–0.0)	−1.0 (−2.0–0.0)	−0.8 (−1.5–−0.1)	0.056
Height z-score	−1.0 (−2.2–0.2)	−1.5 (−2.9–−0.5)	−0.7 (−1.9–0.3)	0.431
Duration of PN (mo)	9.5 (4.2–34)	11 (5.4–59)	8.5 (3.8–25)	0.146
Time after weaning off PN (y)			3.9 (1.6–14)	
Weekly PN infusions		7 (6–7)		
PN calories of total nutrition (%)		73 (12–85)		
Time after last bowel resection (y)	2.9 (1.0–9.0)	0.6 (0.2–2.9)	4.4 (2.4–14)	**<0.001**
SBS/dysmotility disorder (n)	48/7	15/2	33/5	1.000
Remaining bowel				
Small bowel (cm)	47 (25–101)	30 (18–60)	50 (31–108)	**0.031**
Small bowel (%)[a]	26 (17–47)	23 (14–29)	32 (21–50)	**0.046**
Ileum (cm)	0 (0–5)	0 (0–4)	2 (0–18)	0.125
Colon (%)[a]	87 (57–100)	71 (22–100)	95 (68–100)	0.069
ICV preserved (n)	26	6	20	0.249
Small intestinal endostomy (n)	4	3	1	0.083
Serum Citrulline (umol/L)	22 (15–29)	13 (10–23)	24 (18–30)	**0.001**
Serum GLP-1 (ng/mL)	6.0 (4.0–16)	4.1 (2.8–5.1)	6.5 (5.1–21)	**0.005**
Serum GLP-2 (ng/mL)	20 (14–28)	19 (14–25)	20 (14–34)	0.571

Data are median (IQR). GLP; glukagon-like-peptide, SBS; short bowel syndrome.
P-values refer to comparisons between patient groups using Fisher's exact test or Mann Whitney U test. P-values <0.05 are marked bold.
[a] %; percentage of remaining age-adjusted small bowel or colon length.

shorter time since the latest bowel resection, and had shorter remaining absolute and age-adjusted small bowel length compared to patients, who had weaned off PN median 3.9 years before the study. Four patients had a small intestinal endostomy without colic continuity. Fourteen of the patients had undergone autologous intestinal reconstruction surgery, including serial transverse enteroplasty and tapering enteroplasty, median 3.1 (0.2–10) years before. Of them, six were currently on PN and eight had weaned off PN. Other baseline data, including BMI, weight and height z-scores were comparable between patients currently receiving PN and patients weaned off PN.

3.2. Serum GLP-1 and GLP-2 levels in relation to controls, PN-dependency and growth

Serum GLP-2 levels were similarly increased both in patients currently receiving PN [GLP-1 4.1 (2.8–5.1); GLP-2 19 (14–25)] and in patients who had weaned off PN [GLP-1 6.5 (5.1–21); GLP-2 20 (14–34)] when compared to controls [GLP-1 6.4 (3.9–10.7); GLP-2 11.6 (7.0–18.6)] (Fig. 1, Table 1). Serum GLP-1 levels were decreased in patients currently receiving PN, when compared to patients, who had weaned off PN and controls (Fig. 1).

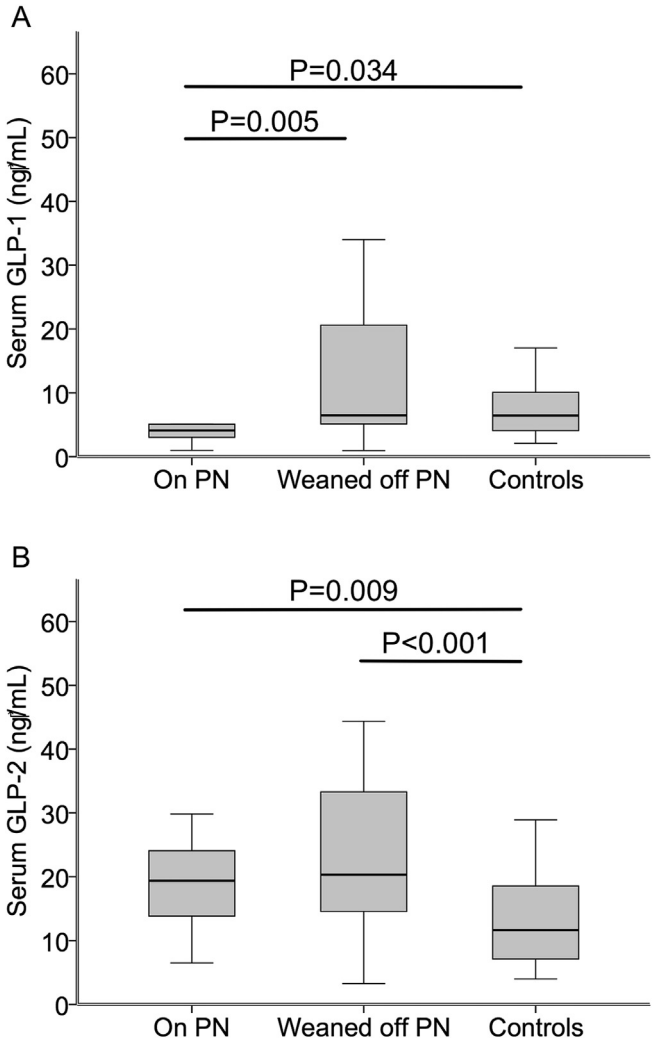

Fig. 1. Fasting serum glucagon-like-peptide-1 (GLP-1) and -2 (GLP-2) levels in patients currently receiving parenteral nutrition (PN), patients weaned off PN and controls. The box plots display median, IQR, and range. P-values for Mann Whitney U test between two groups are shown. Kruskall Wallis test P = 0.017 for GLP-1 and P = 0.001 for GLP-2.

Serum GLP-1 and GLP-2 levels associated with decreasing PN dependency as serum GLP-1 level correlated negatively with percentage of daily parenteral energy and serum GLP-2 with frequency of PN infusions (Fig. 2). During PN, serum GLP-1 levels correlated positively with age (r = 0.794, P < 0.001), time after the latest bowel resection (r = 0.794, P < 0.001), and duration of PN (r = 0.763, P = 0.002), whereas in controls both serum GLP-1 (r = −0.294, P = 0.045) and GLP-2 (r = −0.402, P = 0.007) correlated negatively with age.

In all patients, serum GLP-1 level correlated positively with weight z-score (r = 0.388, P = 0.005). After weaning off PN, weight z-score correlated positively with GLP-1 and GLP-2 (Fig. 3) and BMI with GLP-1 (r = 0.380, P = 0.032). Height z-score was not associated with serum GLP-1 or GLP-2 levels (P > 0.05 for both).

3.3. Serum GLP-1 and GLP-2 levels in relation to remaining intestine

As shown in Fig. 4, serum GLP-2 concentrations were higher in patients with small bowel-colic continuity [21.1 (15.0–30.7) ng/

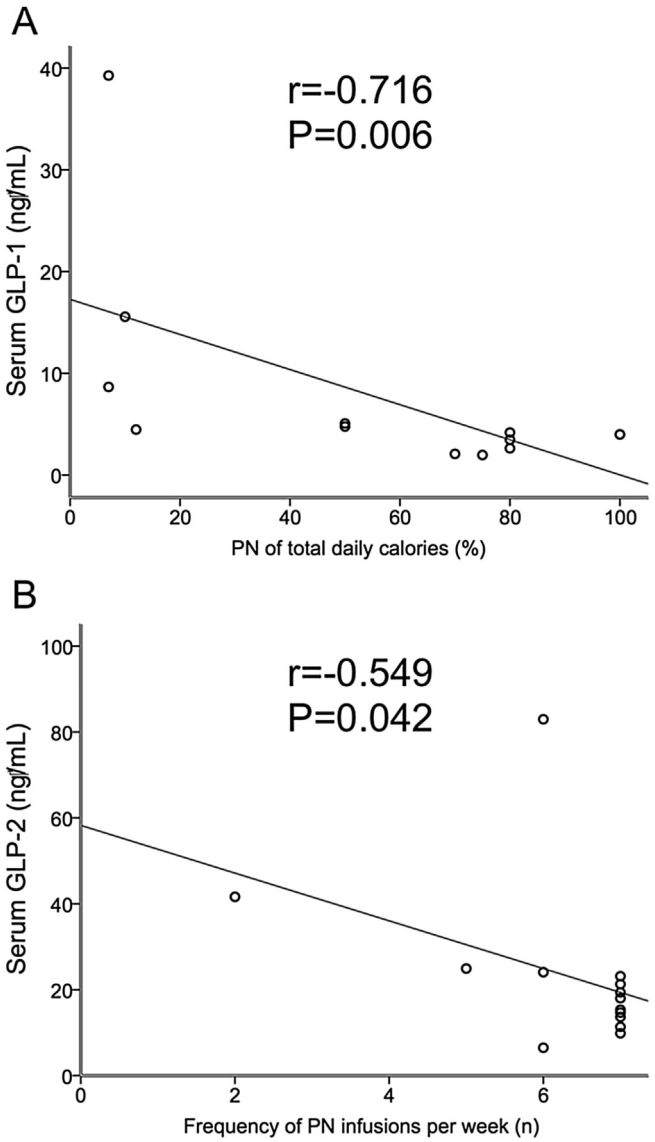

Fig. 2. Serum glukagon-like-peptide-2 (GLP-2) levels correlated with the amount of daily parenteral calories and frequency of parenteral nutrition (PN) infusions. Spearman rank correlations.

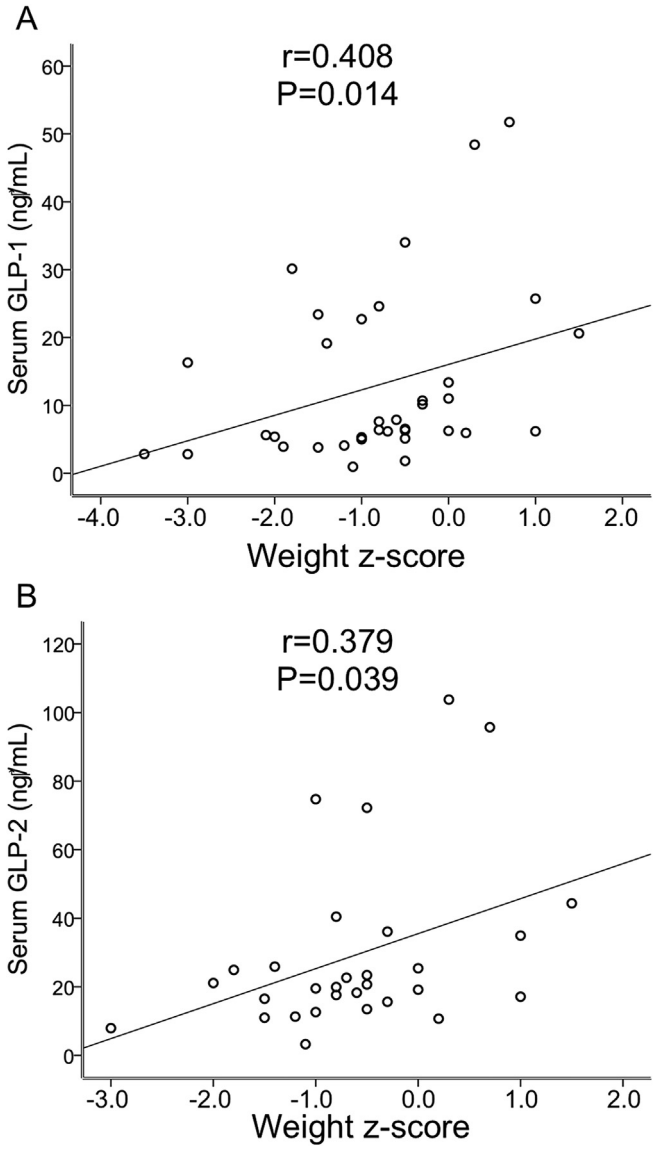

Fig. 3. After weaning off PN, weight z-score correlated with serum glukagon-like-peptide-1 (GLP-1) and -2 (GLP-2) levels. Spearman rank correlations.

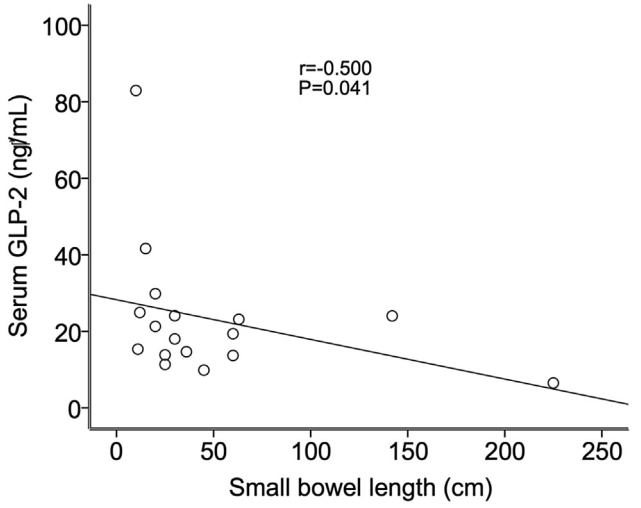

Fig. 4. In patients on PN, serum GLP-2 levels were inversely associated with the remaining small bowel length. A Spearman rank correlation.

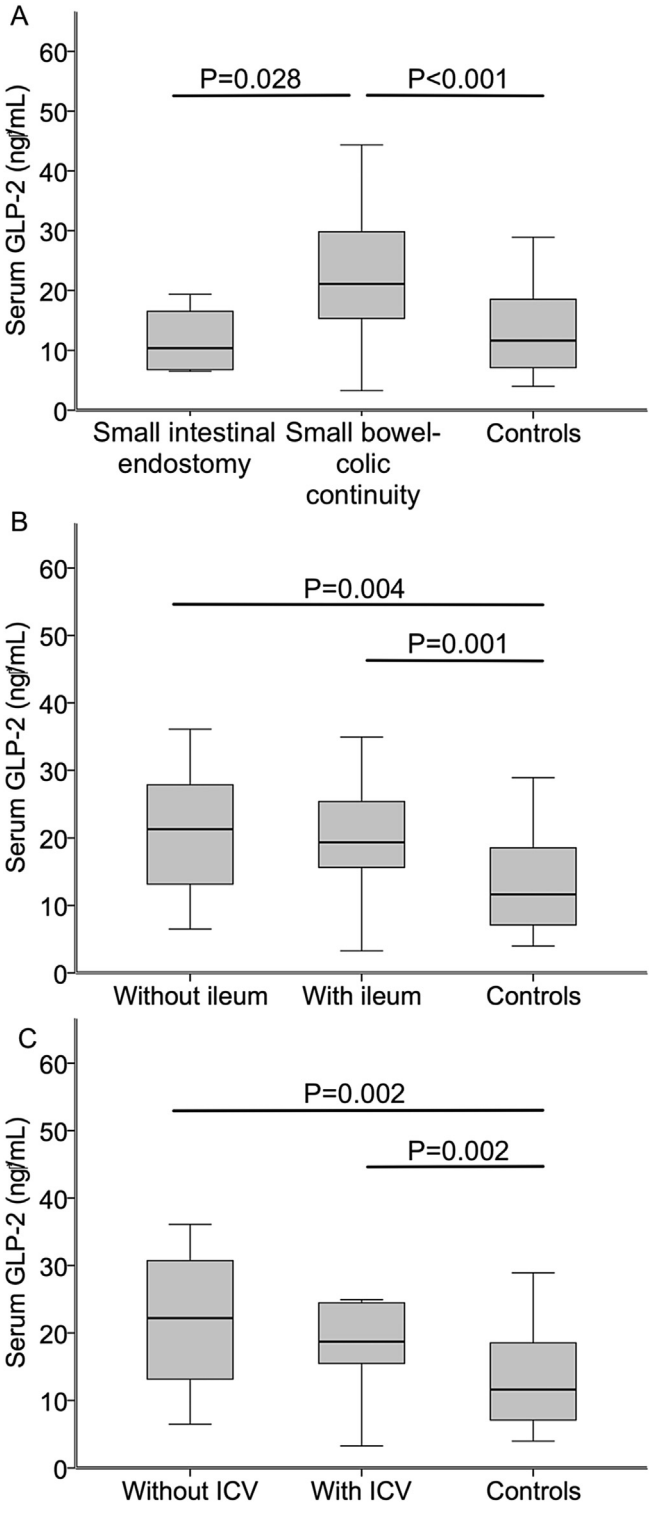

Fig. 5. Patients with small bowel-colic continuity had significantly higher serum glukagon-like-peptide-2 (GLP-2) levels compared to patients with a small intestinal endostomy or controls (A). Patients with ileum with and without ileum (B) and those with or without ileocecal valve, ICV, (C) had comparable levels of serum GLP-2. P-values for Mann Whitney U test between two groups are shown. The box plots display median, IQR, and range. Kruskall Wallis test $P < 0.001$ for all.

mL] compared to patients with a small intestinal endostomy [10.4 (6.6–17.9) ng/mL, P = 0.028]. In patients on PN, serum GLP-2 levels were inversely associated with the remaining small bowel length (r = −0.500, P = 0.041) (Fig. 4), but not with the percentage of remaining colon (r = 0.279, P = 0.197). However, serum GLP-1 and GLP-2 levels were not significantly different between patients with or without any remaining ileum or ileocecal valve (Fig. 5). GLP-1 and GLP-2 levels were comparable between the patients with an anatomical short bowel syndrome and the patients with a primary dysmotility disorder as an underlying etiology of IF (data not shown). Previous autologous intestinal reconstruction surgery had no significant effect on serum GLP-1, and GLP-2 levels (data not shown). During PN, serum GLP-1 levels correlated positively with time after the latest bowel resection (r = 0.765, P = 0.001). Serum GLP-1 or GLP-2 levels showed no significant associations with serum citrulline levels (r = 0.111–0.203, P > 0.05 for all).

4. Discussion

In this cross-sectional study, our major findings were, first, that fasting serum GLP-2 levels are increased in IF patients irrespective of whether or not currently receiving PN and that fasting serum GLP-1 levels are decreased during current PN-dependency, but comparable to controls after achievement of full enteral nutrition following weaning off PN. Secondly, fasting serum GLP-2 concentrations were markedly higher in patients with small bowel-colic continuity than in patients with small intestinal endostomy proportionally to the length of resected small intestine, which may contribute to the positive effects of preserved colon on intestinal adaptation. Our findings support the roles of GLP-1 and GLP-2 in mediating intestinal adaptation after pediatric onset IF.

In animal models and in humans, GLP-2 acts as trophic agent for intestinal mucosa and enhances intestinal nutrient and fluid absorption [9,10,24,25]. After massive bowel resection, serum GLP-2 levels correlate with spontaneous intestinal adaptation in enterally fed animals suggesting that GLP-2 mediates the intestinal adaptive response to resection [11,25,26]. In PN-dependent neonates with IF, Sigalet and colleagues reported positive correlation between serum GLP-2 levels and tolerance of enteral feeds [12]. In adult studies and preliminary data on children, GLP-2 and its long-acting synthetic analog, teduglutide, have been shown to improve nutrient and fluid absorption, weight gain, and to reduce PN requirements [8,13,14]. In this study, serum GLP-1 levels were decreased during PN, while serum GLP-2 levels were increased irrespective of whether or not patients were currently receiving PN. Whether the decreased serum GLP-1 levels during PN are related to limited food intake and nutrient induced secretion of GLP-1 remains unclear and require further studies. Serum GLP-2 levels were elevated not only during PN delivery but also after weaning off PN. This suggests that GLP-2 is not simply associated with the immediate adaptive response after resection, but is also important in the maintenance of the adaptive response. Serum GLP-1 and GLP-2 levels positively associated with decreasing PN requirement as serum GLP-1 levels correlated negatively with percentage of daily PN calories and serum GLP-2 with frequency of daily PN infusions. These observations support the positive effects of GLP-1 and GLP-2 on intestinal adaptation and tolerance of enteral feeds in pediatric IF patients. Additional work on postprandial GLP levels are needed to increase our understanding how meal-stimulated GLP secretion contribute intestinal adaptation in children.

Preserved ileocecal valve and colon improve chances of weaning off PN [3]. In adult short bowel patients with resected ileum, the presence of residual colon associates with increased postprandial serum levels of GLP-1 and GLP-2 [4,5]. In contrast, in premature PN-dependent neonates with IF, no association between the residual colon and serum GLP-2 levels was observed [12]. In this study among children with IF, the remaining small bowel length correlated negatively with the increased serum GLP-2 levels suggesting an enhanced adaptive response in patients with a shorter remaining small bowel. Moreover, serum GLP-2 levels were significantly higher in patients with preserved small bowel-colic continuity than in patients with small intestinal endostomy and fecal diversion, which underlines the importance of luminal nutrients and bile acids in stimulation of GLP-2 secretion from intestinal L-cells [6,11]. Notably, none of our patients were on total PN, but received variable amount of enteral feeds in addition to parenteral support. Based on our findings, the preserved colon was the main source of fasting GLP-2, because preservation of the ileum or the ileocecal valve had no significant effect on fasting serum GLP-2 levels. In summary, elevated GLP-2 levels in IF children with colonic continuity may contribute to the positive effects of a preserved colon on intestinal adaptation and the superior clinical outcomes in this group of patients.

Serum GLP-2 levels remain elevated up to one month after intestinal resection in neonatal IF [12]. This suggests that GLP-2 is not simply associated with the immediate adaptive response after resection, but is also important in the maintenance of the adaptive response [12]. Accordingly in the present study, serum GLP-2 levels were elevated not only during PN delivery and also after weaning off PN. Serum GLP-1 levels were decreased during PN, but elevated to the control level after weaning of PN. Both GLP-1 and GLP-2 serum levels correlated positively with weight z-score. These results suggest an ongoing contribution of GLP-1 and GLP-2 to intestinal adaption process in patients with pediatric onset IF.

This study had some limitations, including the cross-sectional study design, which provides association rather than prove of causality. In addition, the number of patients with an endostomy was limited and postprandial GLP levels were not measured. GLP-2 is secreted from ileal and colonic enteroendocrine L-cells in response to both proximal enteric neuronal signaling and the presence of luminal nutrients and bile acids. To better understand the connections between meal-stimulated GLP secretion and intestinal adaptation, postprandial measurements of serum GLPs would be important by providing mechanistic information of the effects of enteral nutrition in weaned off patients compared to patients on PN. Despite these limitations, this study provides new clinical information on the GLP-1 and GLP-2 levels during intestinal adaptation in pediatric onset IF.

Statement of authorship

Study concept: MP; Study design: AM, MP; acquisition of data: AM, drafting of the manuscript: AM; critical revision of the manuscript for important intellectual content: MP, statistical analysis: AM; obtained funding: MP, study supervision: MP. AM and MP have approved the final article.

Conflicts of interest

The authors have no conflicts of interest.

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